MALIGNANT TUMORS OF THE TESTIS*

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DISCUSSION *by E. M. Butt, M. D., Los Angeles; A. G. Foord, M. D., Pasadena; Zera E. Bolin, San Francisco.*

IN the testes one finds a great variety of malignant and benign tumors ranging from highly undifferentiated, malignant round-cell tumors, apparently uniform in structure, up to complex ones composed of adult tissue. The diversity of opinion existing as to the interpretation and classification of these tumors is as varied as their structure. Even today we find little unanimity of opinion; it seems that the histologic diagnosis and interpretation appear to depend largely upon the personal inclination of the pathologist or surgeon examining the material.

NATURE OF TUMORS OF THE TESTICLE

The controversial nature of these tumors dates back to 1696, when St. Donat first described a complex tumor in a testicle. Johnson, in 1854, first identified elements of all primitive germ layers in one of these tumors, and his findings were confirmed microscopically by Langhans and Kocher in 1877. These observers were the first to lay the basis for an accurate classification according to microscopic study. Several years later, Wilms reviewed the subject and simplified somewhat the complex problem by recognizing the tendency of one element in a teratoma to predominate over others. He was the first to postulate the theory that teratoma were derived in some fashion from sexual cells, and that adenoma, carcinoma and the like arose from the tubular epithelium, while leiomyoma, fibroma and sarcoma were derived from the stroma cells. Later Wilms, upon reëxamining tumors previously considered as homologous, such as carcinoma, chondroma, sarcoma, found derivatives of all three layers in them and revised many of his former conclusions. Pick also observed the tendency of one element to predominate or even suppress all the others.

CHEVASSU'S VIEWS

In 1906 Chevassu agreed in principle that many of these tumors were tridermal in origin, but contended that a large number (about 50 per cent) were homologous, were unrelated to teratoma, and were derived from the spermatocytes rather than embryonal sex cells. He termed these tumors "seminome" (now anglicized to seminoma). His conclusions were based largely upon the fact that the characteristic seminoma cell was identical in morphology with the spermatocytes.

EWING'S CONCLUSIONS

In 1911 Ewing reviewed the subject and published a most important contribution to the pathology of these tumors. He challenged the views of Chevassu, and concluded that practically all testicular tumors were teratomatous. In his article he says: "All common, and nearly all rare tumors of the testes, arise from totipotent sex cells in the neighborhood of the *rete,* whose normal development into spermatogonia has been suppressed, but whose potencies remain intact and ready to express themselves in the various forms of simple or complex tumors. . . . The monodermal forms of these growths represent one-sided developments of tridermal teratoma. Very rarely do stroma, duct cells, interstitial cells, or adult seminiferous tubules give origin to characteristic growths."

In 1925 Hinman, Gibson and Kutzman confirmed Ewing's findings, concluded that the preponderance of evidence was in favor of Ewing's theory, and considered the term seminoma as a misnomer.

THE TWO SCHOOLS OF THOUGHT

From these investigations there has developed two opposing schools of thought. Ewing, Martland, Hinman, Gibson, and others, contend that "for practical purposes there is only one tumor, viz., a teratoma." Chevassu, Schultz, Eisendrath, Bell, and others, contend that, in addition to the heterologous tumors, there are a large number of pure homologous tumors, so-called seminoma.

Unique and convincing arguments, backed by evidence, have been brought forward by proponents of both schools, but it is needless to review them as there is nothing new to add. In the last analysis we have to consider but two types of malignant tumor: the teratoid or mixed tumor, and the apparent unicellular type of tumor, viz., seminoma or embryonal carcinoma.

The entire question as to the pathology and classification of these tumors could be simplified if we would accept Ewing's viewpoint, in that the seminoma merely represents a monodermal overgrowth in a tridermal tumor. It was with this idea in mind that this study was instituted.

A pathologist receiving surgical pathologic material from a good-sized general hospital population is impressed, and to a degree amazed, by the great confusion existing in the general surgeon's mind as to the classification and nomenclature of these tumors, as well as the origin and degree of malignancy of the various types encountered, and the varied and even different choice of therapeutic methods selected. To a degree the rarity of these tumors may be blamed for some of the confusion and lack of information, since they constitute only about 0.5 per cent of all male hospital admissions.

CLASSIFICATION OF HINMAN AND GIBSON

Hinman and Gibson, in their publication, proposed a convenient and satisfactory classification in that it is simple but still includes the essential pertinent facts. They considered all malignant testicular tumors as heterologous in type. A part of their classification dealing with malignant tumors of testes is appended.

II. Heterologous tumors (teratomata).
A. Benign:
(1) Adult teratoid tumors.

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B. Malignant:
(1) Embryonal carcinoma (heterologous elements may be present or have been overgrown).
(a) Trophoblastic (chorio-epithelioma).
(b) Hypoblastic.
(c) Epiblastic.
(d) Seminome (mesoblastic?) (embryonal carcinoma of Ewing).
(2) Sarcomatous mixed tumor (very rare and probably represent one-sided developments of teratoma).

Since the publication of this classification, I have preferred to follow it, recording diagnoses as malignant teratoma of testis, seminoma variety; or malignant teratoma, adenocarcinomatous in type, etc., or using some such qualifying phraseology as applied to different tumors, thus informing the surgeon as to the type of tumor he is dealing with. This information is important, as there appears to be vital clinical, pathologic and biologic differences in the various varieties, particularly as to the mode of development, and rapidity and structure of primary metastases; period of expectancy, radiosensitivity, and behavior of Prolan A (follicular ripening hormone of the anterior pituitary) output in the urine.

FERGUSON'S CONTRIBUTION ON THE BIOLOGIC PHASES

Ferguson's valuable contribution on the biologic phase of the subject of testicular tumors deserves especial mention. He finds that the Prolan A content of the urine varies in proportion to the embryonal character of the tumor, and thus in relation to the structure of the tumor. He classes tumors, according to amount of hormone excretion, in the following order: (1) chorio-epithelioma, (2) embryonal adenocarcinoma, (3) embryonal carcinoma with lymphoid stroma, (4) seminoma, (5) teratoma with adult characteristics. From these investigations he has been able to work out a definite, quantitative relationship existing between the degree of radiosensitivity to the excretion of Prolan A, thus: the greater the amount of hormone excreted, the more sensitive the tumor. He is also of the opinion that a quantitative biologic assay is a more valuable index as to radiosensitivity than histologic interpretation.

His investigations show that not only can a diagnosis of the primary tumor or occurrence of metastases be determined by assay of hormone excretion, but that it is also of value in differentiating the various types of teratoma. The hormone excretion level varies in different varieties of teratoma as follows:

Chorio-epithelioma, 50,000 or more mouse units per liter.
Embryonal adenocarcinoma, 10,000-40,000 mouse units per liter.
Embryonal carcinoma with lymphoid stroma, 2000-10,000 mouse units per liter.
Seminoma, 400-2000 mouse units per liter.
Adult teratoma, 50-500 mouse units per liter.

It seems significant that all these varieties of tumors, including even the seminoma, give rise to Prolan A, and that they fall in such well-defined groups. The mechanism of the hormone production is not definitely understood, even in pregnancy. It reaches its highest concentration in chorio-epithelioma, both in the female following pregnancy and in chorio-epithelioma testis, where the type cell is predominantly trophoblastic. The specific hormone is also excreted in the urine in certain other tridermal tumors, but in very few if any extragenital malignant tumors in the male. Thus it seems that its presence in testicular tumor cases is presumptive evidence of the tridermal origin of these tumors.

Prolan A determinations have been performed in only four of these cases, so that data is insufficient to include in this report.

MATERIAL USED IN THIS ANALYSIS

The basis for this report is a histopathologic analysis of seventeen primary testicular tumors to determine the frequency with which the characteristic seminoma cell occurred in association with tridermal elements in heterologous tumors and, conversely, to determine the incidence, degree and variety of heterologous elements in the so-called homologous (seminoma) tumors. At first it was intended to include twenty-five tumors, but some of the material was derived from metastases obtained at autopsy in which the primary tumor was not available.

It may be in order to relate a few interesting facts concerning these cases. It is significant that the seventeen patients were operated upon by fourteen different surgeons; one surgeon removed three and another removed two of the tumors. Simple castration was done in each instance, and the greater number were given postoperative irradiation. Only one patient was subjected to preoperative irradiation, viz., the chorio-epithelioma case, who is now alive and evidently well at the end of five years and three months. Of the entire series eleven are dead, six are living, but of these, two have only been recently (one and two months) operated upon. All cases were subjected to the same operative treatment, and for general purposes to the same radiation technique; and yet no two cases were identical histopathologically, whether surviving or dead. (See Chart 1).

INTERPRETATION OF THE CHART

On the accompanying chart are recorded the various mesoblastic, hypoblastic and epiblastic representatives, as well as the trophoblastic elements and characteristic seminoma cells found in each tumor. An attempt was made to estimate and list them according to relative percentage incidence; thus the symbol ++++ indicates that this element or elements were predominant.

A simple glance at the chart will acquaint one with the remarkable structural variations encountered. The greater number fall in the group of embryoid tumors, in which either the hypoblastic elements or the characteristic "seminoma" type of cell appear to play the dominant part in conferring malignant potentialities. The term "seminoma cell" is used in a general descriptive sense only; no attempt is made to classify it.

Not a single adult embryoma was found.

The term "teratoma" should be applied only to tumors composed of elements derived from all

CHART 1.—*Tumors of the Testicle*

No.	Age	Mesoblastic		Hypoblastic		Epiblastic		Trophoblastic	Seminoma
		Benign	Malignant	Benign	Malignant	Benign	Malignant		
1	26	+	+	++	++++	++	+	+	+
2	26	++	0	+	++	++	+	+	++++
3	38	0	0	+	0	+	0	Trace	++++
4	29	+	+	++	+++	+	+	0	Trace
5	29	0	0	0	+	0	0	++++	0
6	31	+	+	+	++	+	0	+	+
7	23	+	0	++	++++	+	0	0	+
8	27	++	0	+	+++	+	0	0	+++
9	20	++	0	+++	0	+	0	0	+
10	P	++	+	+++	0	++	0	0	0
	36								
	M	+	0	+	+++	+	0	0	+
11	37	0	0	0	+	0	0	0	++++
12	36	0	0	+	0	+	0	0	++++
13	33	+	0	+	++++	+	0	+	0
14	47	0	0	0	+	0	0	0	++++
15	35	0	0	0	+	0	0	0	++++
16	28	+++	0	++	+	+++	0	0	+
17	33	0	0	0	0	0	0	0	++++

P. Primary tumor.
M. Metastatic tumor.

three primary germ layers. In these malignant complex testicular tumors representative elements of only two layers, and occasionally only one layer, are usually found, so the term "teratoid" is preferable over the rigid term "teratoma."

In this series we find seven cases which could be considered as monodermal tumors, depending upon the inclination of the observer, the characteristic seminoma type of cell predominating; but in six of the seven cases representatives of one or more primary germ layers were also present in some degree, and only in one instance were they not found (Case 17). Thus it seems that we have only one monodermal tumor or seminoma. Conversely, in the teratoid group, comprising ten of the number, characteristic seminoma cells in varying amounts were found in every case except one. In the seventeen primary tumors, seminoma cells were found in all but two, one being trophoblastic. This characteristic cell was present irrespective of whether the predominating elements were epiblastic, hypoblastic, or mesoblastic. It seems that in the smaller seminoma type of tumor tridermal elements were more abundant and more easily found than in the larger ones, thus bearing out Ewing's view, that in the larger seminomata the tridermal elements are crowded out—probably because of the rapid growth capacity of this cell.

In this group we find only one apparently pure or homologous seminoma type tumor (No. 17) and five (Nos. 3, 11, 12, 14 and 15) almost pure seminomatous tumors. In two cases (Nos. 2 and 8), although seminoma cells were in abundance, other elements from one or more primitive germ layers were represented in differing degrees and in varying grades of complexity, so as to leave no question as to their teratoid origin. In the chorio-epithelioma a small amount of adenocarcinoma was found. Only one tumor (Case 6) was found in an undescended testicle.

Since the greater number of testicular tumors show highly variable complex histologic characteristics and considerable variation in individual germ-layer representation in different specimens, and even in different portions of the same specimen, it is unwise to examine only single, or two or three sections in a given tumor and attempt to draw conclusions. One cannot obtain a true interpretation except from multiple sections. In Case 10, originally only a part of the primary tumor was received for examination; history was not available. Multiple sections were made, and only benign or differentiated mesoblastic, hypoblastic and epiblastic elements were found, and so a diagnosis of probable benign teratoid tumor was given. Later another specimen was received labeled "retroperitoneal tumor," and examination of this revealed malignant hypoblastic representatives as well as other elements, and even islands of characteristic seminoma cells.

In these tumors, cells from the individual primitive germ layers may proliferate at different times and stages of development and at different rates, so that it is hazardous to attempt to predict which element or elements will predominate in either the primary tumor or its metastases.

IN CONCLUSION

Perhaps no definite conclusions can be drawn from this study, which covers only a compara-

tively few cases; but at least one is justified in inferring that the greater number, if not all, malignant tumors of the testicle are primarily tridermal in origin, and for practical purposes can and should be considered as such.

I am of the belief that pure homologous (so-called monodermal or seminoma) tumors do not exist, and that if this type of tumor is subjected to severe histopathologic analysis, it will be found to represent merely an overgrowth of one malignant element at the expense of all other blastodermic derivatives. This contention is substantiated by the demonstration of representatives of one or more blastodermic derivatives in all the tumors in this series with one exception, whether the predominant type of cell was adenocarcinomatous or seminoma in type.

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DISCUSSION

E. M. Butt, M. D. (3551 University Avenue, Los Angeles).—Doctor Maner's paper emphatically recalls to our attention that the majority of malignant tumors of the testicle are teratoid in origin, tridermal in constitution, and not homologous or single-cell tumors arising from adult tissues. This is an old problem that has been studied by such able men as Ewing, Wilms, Pick, Hinman, and others. These investigators have produced an overwhelming amount of evidence to refute the contentions of Chevassu in regard to the histogenesis of the tumor, which he has termed "seminome." Furthermore, the works of these men have served greatly to simplify the classification of tumors of the testis. And yet one cannot help being impressed with the confusion that prevails as a result of the diversity of opinions regarding this subject, as are recorded in the literature and some textbooks. This confusion clearly emphasizes the need of such papers as Doctor Maner's and, too, the need of subjecting testicular tumors to an accurate histopathologic study.

It is important to note that in eight of the tumors of the testis reported by Doctor Maner, the predominating cell type is the cell of the "seminome," and that seven of these tumors contain heterologous elements. Furthermore, it is noted that in seven of the seventeen tumors "seminome" cells are found associated with predominating hypoplastic or epiblastic elements. These facts serve to establish beyond a doubt that the "seminome" of Chevassu is of teratoid origin.

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A. G. Foord, M. D. (Pasadena Hospital, Pasadena).—Doctor Maner's presentation as to the nature and pathologic histology of testicular tumors is marred by two noteworthy omissions. First, he has modestly neglected to state that he studied thousands of microscopic sections before he was able to find that sixteen out of seventeen cases showed other tissue elements than the usual seminoma cell. This is particularly important, since the usual practice in the routine examination of tumors is to section a few blocks and diagnose from these as to the histologic components of the tissue. Second, he has neglected to state definitely what he means by the terms mesoblastic, hypoblastic, epiblastic, and trophoblastic. I trust that he will cover this in his discussion, in order that the pathologist who is not particularly inclined embryologically can thoroughly appreciate the microscopic components included in Chart 1. From my own experiences, I believe that Doctor Maner's final deductions are sound, and that Ferguson's work biologically supports his view. However, from the standpoint of the individual patient, I fear that, so far, fine points of histologic studies have added little to the ultimate prognosis; but it is hoped that further advances in radiology will come to our aid. The first step, naturally, is the continued proper histologic analysis of the testicular tumors, as has been done in this paper, and later correlation of the clinical results from surgery and radiation in the various types of tumor.

Zera E. Bolin, M. D. (490 Post Street, San Francisco).—Tumors of the testes, theoretically, may arise from the sperm cells in any stage of their development; from the tubular epithelium; from the stroma; or from the blood vessels or nerves. Practically, however, there is seen but one malignant tumor of the testes. This has been divided by surgeons into teratoma and seminoma. I do not agree with the view of Chevassu that the so-called seminoma arise from spermatocytes. I believe no one has shown, histologically, that such a relationship exists. I agree thoroughly with Doctor Maner that there is only one tumor of the testes, and that this should be classed in the teratoma group. I think that Doctor Maner has proved his point by his method of taking multiple sections. In a series of testes removed at necropsy and subjected to intensive examination, 1.2 per cent of all organs examined revealed the presence of small tumors which were histologically teratomatous in nature.

It is of extreme interest, along the line of the Prolan A test, that Ferguson was able to obtain a positive assay in all of his testicular tumors. I believe that Doctor Maner has settled the argument and that we can conclude that the so-called seminoma does not exist as a tumor entity. I believe that we can all subscribe to the belief that the various tumors are developments from teratoma with a one-sided proliferation. Incidentally, it is interesting to note that the type of operation, in most of these cases, was orchidectomy and orchidectomy only.

THE SUBTHYROID CHILD*

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Discussion *by Donald K. Woods, M. D., San Diego; Helen Pryor, M. D., Palo Alto; Henry E. Stafford, M. D., Oakland.*

IT is not the purpose of this paper to discuss all the various manifestations, signs, and symptoms of hypothyroidism in children; but rather to enumerate some of the clinical signs and symptoms, and to discuss some of the laboratory means available for making a diagnosis of hypothyroidism. It is of paramount importance that hypothyroidism in children be detected early, in order that treatment be instituted before rehabilitation becomes too limited.

The growth and development of the child is dependent on an adequate source of diet, vitamins, and a proper balance of endocrine hormones.

ENDOCRINE INFLUENCE ON GROWTH AND DEVELOPMENT

The voluminous literature devoted to growth and development, from the endocrine standpoint, is quite disconcerting to one who wishes to be conservative in his diagnosis and treatment of hypothyroidism.

Perhaps more voluminous has been the literature on the relation of vitamins to growth and development, with comparative delineations of white rats fed or deprived of certain vitamins.

It is to be expected, then, that a real doctor's dilemma has perhaps resulted, since both vitamins and endocrines are vying for first place in the development and nutrition of the child.

Science has proved the merit of vitamin B as essential for the growth and development of ani-

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